Journal of Neurology (2018) 265:2861–2874
https://doi.org/10.1007/s00415-018-9057-7

ORIGINAL COMMUNICATION

Therapeutic regimen of L-arginine for MELAS: 9-year, prospective, multicenter, clinical research

Yasutoshi Koga[1] · Nataliya Povalko[1,2] · Eisuke Inoue[3] · Hidefumi Nakamura[4] · Akiko Ishii[5] · Yasuhiro Suzuki[6] · Makoto Yoneda[7] · Fumio Kanda[8] · Masaya Kubota[9] · Hisashi Okada[10] · Katsunori Fujii[11]

Received: 3 July 2018 / Revised: 7 September 2018 / Accepted: 8 September 2018 / Published online: 29 September 2018

Abstract

Objective To examine the efficacy and safety of the therapeutic regimen using oral and intravenous L-arginine for pediatric and adult patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS).

Methods In the presence and absence of an ictus of stroke-like episodes within 6 h prior to efficacy assessment, we correspondingly conducted the systematic administration of oral and intravenous L-arginine to 15 and 10 patients with MELAS in two, 2-year, prospective, multicenter clinical trials at 10 medical institutions in Japan. Subsequently, patients were followed up for 7 years. The primary endpoint in the clinical trial of oral L-arginine was the MELAS scale, while that for intravenous L-arginine was the improvement rates of headache and nausea/vomiting at 2 h after completion of the initial intravenous administration. The relationships between the ictuses of stroke-like episodes and plasma arginine concentrations were examined.

Results Oral L-arginine extended the interictal phase ($p = 0.0625$) and decreased the incidence and severity of ictuses. Intravenous L-arginine improved the rates of four major symptoms—headache, nausea/vomiting, impaired consciousness, and visual disturbance. The maximal plasma arginine concentration was 167 µmol/L when an ictus developed. Neither death nor bedriddenness occurred during the 2-year clinical trials, and the latter did not develop during the 7-year follow-up despite the progressively neurodegenerative and eventually life-threatening nature of MELAS. No treatment-related adverse events occurred, and the formulations of L-arginine were well tolerated.

Conclusions The systematic administration of oral and intravenous L-arginine may be therapeutically beneficial and clinically useful for patients with MELAS.

Keywords L-Arginine · Mitochondrial disease · MELAS · Stroke-like episodes · Ictus

✉ Yasutoshi Koga
yasukoga@med.kurume-u.ac.jp

[1] Department of Pediatrics and Child Health, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0001, Japan

[2] Institute of Fundamental Medicine and Biology, Open Lab Gene and Cell Technology, Kazan Federal University, Kazan, Russia

[3] Division of Medical Informatics, St. Marianna University School of Medicine, Kawasaki, Japan

[4] Center for Clinical Research and Development, National Center for Child Health and Development, Setagaya, Japan

[5] Department of Neurology, Tsukuba University School of Medicine, Tsukuba, Japan

[6] Department of Pediatric Neurology, Osaka Women's and Children's Hospital, Osaka, Japan

[7] Department of Neurology, Faculty of Nursing and Social Welfare Sciences, Fukui Prefectural University, Fukui, Japan

[8] Department of Neurology, Kobe University Hospital, Kobe, Japan

[9] Division of Neurology, National Center for Child Health and Development, Setagaya, Japan

[10] Department of Neurology, Nagoya Medical Center, Nagoya, Japan

[11] Department of Pediatrics, Chiba University Graduate School of Medicine, Chiba, Japan